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IMPORTANT ANNOUNCEMENT

The increase in the output of papers in the field of mathematical biophysics makes it difficult to insure prompt publication without an increase in the size of the journal. Therefore, the Bulletin of Mathematical Biophysics inaugurates the following service:

Upon acceptance of a paper, the Editor, if necessary, will ask the author to shorten the paper to an extent dictated by the requirements of a reasonably prompt publication. The shortening should in no case reduce the paper to a mere abstract. Such a shortened paper will be published within six months or less.

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All papers in the Bulletin which have been thus shortened, will be marked at the end by the symbol MF, followed by a figure, indicating the number of doublespaced typewritten pages of the unabbreviated manuscript.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 3, 1941

A NEURAL MECHANISM FOR DISCRIMINATION IV: MONOCULAR DEPTH PERCEPTION

HENRY E. STANTON
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The mechanism for discrimination described by A. S. Householder is applied to the problem of monocular depth perception and the Weber ratio is determined. The ratio obtained varies as a small positive power of the distance for nearby objects, while for distant objects it is indicated that discrimination is relatively impossible.

In a previous paper, A. S. Householder (1939) has described a hypothetical neural mechanism for discrimination, which had the property of diverting to different neural pathways responses to stimuli of different intensities. In a later paper (1940) the mechanism was applied to the monocular discrimination of lengths which were placed at right-angles to the line of sight, and also to binocular depth perception. (These papers will be referred to hereafter as I and III respectively.) In both of these cases, the problem was formulated in terms of stimuli which, if acting alone and uninhibited, would cause a rotation of the eye, and the responses of such stimuli entered the mechanism of discrimination.

The object of this paper is to apply this same mechanism to another type of discrimination, that of monocular depth perception. In this problem, the change in shape of the crystalline lens during the process of accommodation of the eye and the resulting changes in muscle tension in the ciliary body are assumed to bear the same relation to the action of the discrimination mechanism as the rotations of the bulbus as discussed in III.

It is, therefore, necessary to make some sort of mathematical estimate of the changes in shape of the lens as different points on the axis of the eye are fixated in order to determine the changes in muscle tension and find the associated Weber function. Only one eye will be considered. The problem seems to be naturally divided into two parts, (1) the determination of the change in equatorial diameter as a function of the radius of curvature of the anterior surface of the lens, and (2) the determination of the functional dependence of the radius of curvature on the distance of a given point from the eye.

1. *The determination of the change in equatorial diameter as a function of the anterior radius of curvature.* In Figure 1, an approxi-

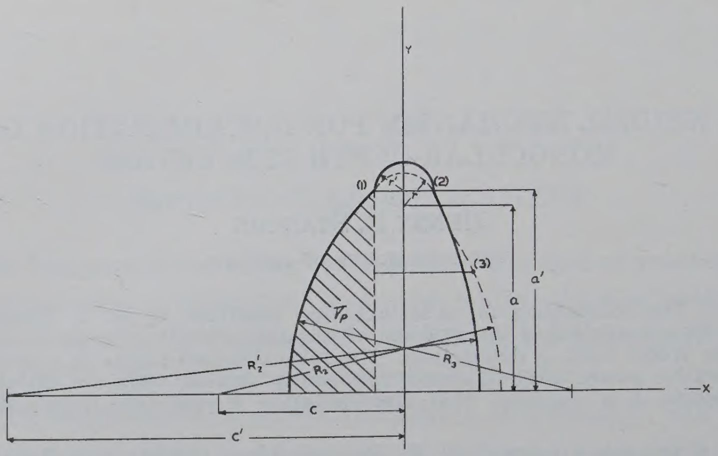

FIGURE 1

mate cross section of the lens is shown in the position of partial accommodation, and this diagram essentially contains most of the geometrical assumptions made for mathematical simplicity. According to W. S. Duke-Elder (1932), in the relaxed position both the anterior and posterior surfaces of the lens are spherical. When in the accommodated position, the posterior surface changes only slightly in curvature, and will be considered as not changing in this analysis. The anterior surface changes very markedly in curvature and moves forward. The exact nature of the surface which connects the anterior spherical cap with the equatorial region is not too definitely specified, but indications are that it is practically a cone and has been assumed so here. In addition it has been assumed that throughout the range of accommodation, points (1) and (2) remain stationary while point (3) moves in such a way that the slope of the line (2)-(3), which is an element of the cone, remains fixed, the whole process taking place at constant volume of the lens.

In discussing these approximations, they are introduced necessarily to make the problem sufficiently simple so that it can be solved explicitly, and some of them are highly doubtful, although the final answer may not be nearly as far from the truth as the original assumptions are. In particular, according to most students, point (2) does not remain even approximately stationary. This point will be common to all possible configurations of the surfaces, whereas it is generally assumed that there is no such point, that is, the point corresponding to it would move with the changes. Also the equatorial region is probably not circular in cross section, but is frequently drawn parabolically. The assumptions regarding the conical surface are probably a greatly over-simplified picture, but the effects on the computations will not be greatly altered by more complicating assumptions in regard to this surface. The important portion of the whole problem is the equatorial belt, since it is a result of the deformation of this portion which is responsible for the discrimination, and this fact must be remembered in any approximation. Unfortunately, there does not seem to be very much available literature on the precise geometry of the lens in these parts.

The problem, then, is one of finding the equatorial radius $a + r$ as a function of R_2, the radius of curvature of the anterior surface. Since it is assumed that the posterior surface does not change in shape, the volume V_p can be neglected, and the evaluation of the volume of the rest of the lens can be considered. For this purpose, the lens is assumed to be divided into three parts V_1, V_2, V_3 as shown. If K is the slope of the line connecting points (2) and (3), then

$$\frac{y_2 - y_3}{x_2 - x_3} = -\tan\theta = K = \frac{y_2 - y}{x_2 - x}. \tag{1}$$

If points (1) and (2) are symmetrical about the y-axis, then from the equation of a circle for the curve bounding V_3,

$$(y - a)^2 + x^2 = r^2, \tag{2}$$

from which it follows that

$$(y_1 - a)^2 + x_1^2 = (y_2 - a)^2 + x_2^2 = r^2. \tag{3}$$

Another relation is required in order to have a determinate problem to connect the coordinates of the points (1) and (2), and various assumptions can be made at this point. A very simple one is the assumption of symmetry described above whereby

$$\begin{aligned} x_2 &= -x_1 = r' \\ y_2 &= y_1 = a', \end{aligned} \tag{4}$$

r' and a' being the values associated with the relaxed position of the lens for the quantities a and r.

The coordinates of the point (3) can be determined as functions of c and R_2 quite simply, since the circle is assumed tangent to the line segment at this point,

$$\begin{aligned} y_3 &= R_2 \cos\theta, \\ x_3 - c &= R_2 \sin\theta, \end{aligned} \tag{5}$$

where from (1)

$$\cos\theta = \frac{1}{\sqrt{1+K^2}},$$
$$\sin\theta = -\frac{K}{\sqrt{1+K^2}}. \tag{6}$$

Another relation is obtained by substituting (5) into (1),

$$R_2 = \frac{y_2 - K(x_2 - c)}{\sqrt{1+K^2}}, \tag{7}$$

which gives R_2 as a function of c and the parameter K.

It is now possible to calculate the volume of the lens having located the important points which are the limits of integration. The lens is a solid of revolution and consequently a convenient element of volume can be defined as

$$dV = 2\pi y[f_1(y) - f_2(y)]dy\,, \tag{8}$$

where $f_1(y)$ and $f_2(y)$ are the appropriate equations of the bounding curves in Figure 1.

According to the assumption of constant volume it follows that

$$\delta(V_1 + V_2 + V_3) = 0\,, \tag{9}$$

and because of the manner of selecting these volumes, V_1 and V_2 can be considered functions of R_2 alone and V_3 a function of a only, and so this last equation implies that

$$-\frac{dV_1}{da} = \frac{dV_2}{dR_2} + \frac{dV_3}{dR_3}. \tag{10}$$

These volumes can be computed from the equation

$$V = 2\pi \int [f_1(y) - f_2(y)]\, y\, dy \tag{11}$$

and then differentiated with respect to the proper variable in each case and substituted into (10), thus establishing a functional relationship between R_2 and a of the form

$$f(R_2) + g(a) = 0\,. \tag{12}$$

This expression, theoretically, can be solved for a as a function of the radius, but practically this is entirely too cumbersome, and approximations will be used. A very simple type of approximation is to find the derivative, i.e.

$$\frac{da}{dR_2} = -\frac{f'(R_2)}{g'(a)} \tag{13}$$

and then replace the differentials by the corresponding difference values, which gives

$$a_1 - a_2 = -\frac{f'(R_2')}{g'(a')}\,(R_{2_1} - R_{2_2})\,. \tag{14}$$

The primed values in this expression are assumed to be those corresponding to the relaxed position, and this relation will be assumed to give the dependence of the equatorial diameter of the lens upon the radius of curvature of the anterior surface. If the computations are carried on in a straightforward manner, the final result turns out to be

$$a' - a = -\frac{2R_2\left[1 + \dfrac{2K^2+1}{2K\sqrt{1+K^2}}\right]}{\pi a' + 4r'}\,(R_2' - R_2)\,, \tag{15}$$

which, for simplicity can be written in terms of suitable parameters.

$$a = V - W R_2\,. \tag{16}$$

2. *The determination of the radius of curvature as a function of the object distance.* In Figure 2 an approximate cross section of the complete optical system of the eye is indicated as far as rays which are close to the optical axis are concerned, together with the assumed coordinate system. The object of the complete system is located at x_0 and the image is formed on the retina, the latter distance being fixed. The procedure adopted here was to compute the images and objects for the successive surfaces using the image of the surface

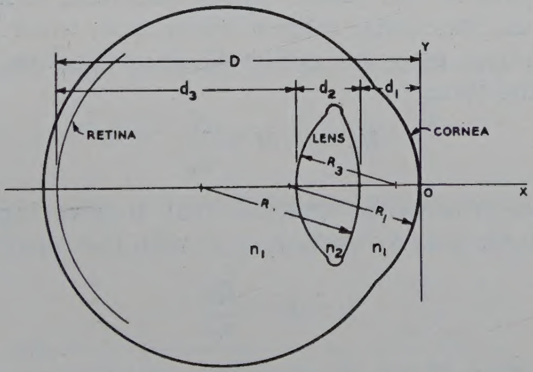

FIGURE 2

immediately preceding as the object of the surface under consideration and subsequently finding its image according to the well known formula

$$\frac{n_2}{v} - \frac{n_1}{u} = \frac{n_2 - n_1}{R_2}. \tag{17}$$

The radius of any surface is considered negative if it is convex toward the right. The image and object distances are the coordinates in the assumed frame and can be either positive or negative. The quantities to be substituted for the three surfaces are,

surface	1	2	3
object distance, u	x_0	$x_1 - d_1$	$x_2 - P$
image distance, v	x_1	$x_2 - d_1$	$D - P$

where

$$P = d_1 + d_2 \tag{18}$$

represents the position of the posterior pole of the lens which is assumed to remain constant or fixed. In these relations, there are only three variables, x_0 which is the independent variable, R_2 and d_1.

A functional relationship can be established between R_2 and d_1 from the first part of this paper. These quantities when substituted into (17) and the functional relation mentioned, which is linear to a first approximation, give the radius R_2 as a function of the single variable x_0 of the form,

$$R_2 = -M + \frac{N}{x_0}, \tag{19}$$

and this may be used with equation (16) to give the value of the equatorial diameter a as a function of x_0 with the form,

$$a = P - \frac{Q}{x_0}. \tag{20}$$

3. *Application of the discrimination mechanism.* The parameters P and Q can be considered as fixed constants which are determined by the geometry of the eye in the relaxed position and they are both positive. Since a is also to be considered positive, the formula applies only for such values of x_0 for which the second term remains smaller than the first. This point of breakdown of the theory can well be anticipated, but this will occur only for points a few millimeters in front of the cornea.

In applying the mechanism described in III, an identical mechanism can be considered as operative in connection with the ciliary muscles which are supposed to give the accommodation. In this case the contraction of the muscle which is proportional to the change in radius a of the lens is assumed proportional to the activity of center C_2 and this will lead to the expression

$$u = v(a_0 - a) \tag{21}$$

where u denotes the stimulus intensity, v is a coefficient, and where a_0 would be the value of the radius of the lens in the relaxed position, i.e. in the absence of any stimulus. This expression is quite analogous to equation (14) in that paper and derived in the same manner. Then, if δ is the Weber ratio for u and Δ corresponding ratio for x_0, it follows that

$$u + \delta u = v(a_0 - P + \frac{Q}{x_0 + \Delta x_0}) \tag{22}$$

from (72). Hence

$$\delta u = v\left[\frac{Q}{x_0 + \Delta x_0} - \frac{Q}{x_0}\right]. \tag{23}$$

But from (11) of III,

$$\delta = \beta u^{-\alpha}, \tag{24}$$

where α has some value between 1/2 and 1/3. Hence

$$\delta u = \beta u^{1-\alpha} = \beta v^{1-\alpha}(a_0 - P + \frac{Q}{x_0})^{1-\alpha}. \tag{25}$$

This may be equated to (23) and the equation solved for Δx_0, which turns out to be

$$\Delta x_0 = -\frac{x_0{}^2 \frac{\beta}{Q} v^{-\alpha}(a_0 - P + \frac{Q}{x_0})^{1-\alpha}}{1 + x_0 \frac{\beta}{Q} v^{-\alpha}(a_0 - P + \frac{Q}{x_0})^{1-\alpha}}. \tag{26}$$

Assuming that a_0 corresponds to the relaxed position, it becomes equal to P and this equation simplifies to

$$\Delta x_0 = -\frac{\rho x_0^{1+\alpha}}{1 + \rho x_0^{\alpha}}, \tag{27}$$

where

$$\rho = \frac{\beta}{Q} v^{-\alpha} Q^{1-\alpha}. \tag{28}$$

The presence of the minus sign perhaps requires explanation. The formula, in fact, predicts the amount by which an object must be moved *closer* to the subject in order that it may be recognized as closer, since moving the object closer results in an increase in the intensity of the stimulus (deviation of the lens from the relaxed position).

It is to be noted that for x_0 sufficiently small, i.e. for objects sufficiently close, the J. N. D. will have the approximate value

$$\Delta x_0 = -\rho x_0^{1-\alpha}, \tag{29}$$

while as x_0 increases, Δx_0 approaches x_0 in numerical value, while remaining always numerically less. The interpretation of this is that only relatively near objects can be distinguished monocularly as to depth—which is, indeed, almost self-evident.

The writer is indebted to Dr. A. S. Householder for assistance in the preparation of this paper, especially concerning the biological aspects.

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SOME PRELIMINARY CONSIDERATIONS CONCERNING CONCENTRATION OF OXYGEN IN TISSUE

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An approximate expression for the average concentration of oxygen in vascular tissue is derived on the basis of certain assumptions. These assumptions are then analyzed, and the inadequacies of the approximate derivation are pointed out; possibilities as to the method and results of more exact derivations are briefly discussed.

The problem of what factors influence the concentrations in tissue of capillary-supplied substances, especially oxygen, was first suggested to the writer by Dr. Melvin H. Knisely of the University of Chicago, in connection with the variations in blood-flow rates during malaria. In this paper the writer is attempting merely to outline the quantitative aspects of capillary production of metabolites, and to derive an approximate expression for the average concentration of oxygen in a tissue. He realizes that the treatment here given is by no means complete, but hopes that it may, in the future, be made more exact and extended to concentrations of other substances than oxygen.

Oxygen is supplied to respiring cells in tissue by the blood; some of it exists in the blood in chemical combination with the hemoglobin in erythrocytes, while some is in solution in the plasma. While the blood is passing through a capillary, the dissolved oxygen diffuses through the thin capillary wall into the surrounding tissue, where it is consumed. Meanwhile, the oxidized hemoglobin in the blood cells is giving up some of its oxygen to help maintain the concentration of dissolved oxygen.

Obviously the rate of diffusion through the wall of a given capillary will depend on several factors:

x_1, x_2 = the concentrations, in gm. per cc. of blood, of oxygen in arteriolar and venular hemoglobin, respectively.

c_1 = the concentration, in gm. per cc., of dissolved O_2 in the arteriole.

c_2 = the concentration, in gm. per cc., of dissolved O_2 in the capillary just before it empties into the venule. We are not letting c_2 be venular concentration, because in the venule blood from several capillaries is mixed, and the effect of the capillary in question is no longer distinguishable.

$h =$ the permeability of the capillary wall to diffusing O_2.

$D =$ the average tissue diffusion coefficient for O_2.

$-q =$ the rate of O_2 consumption in gm. per cc. per sec., in the tissue.

$v =$ the velocity of blood flow in the capillary.

$l =$ the length of the capillary from arteriole to venule.

$r_0 =$ the radius of the capillary.

$d =$ the average distance to adjacent capillaries.

For the present, we simplify matters by making certain assumptions and approximations: We assume that the capillaries in this particular tissue are parallel (this condition is approximately realized in striated muscle). We further assume that a capillary supplies oxygen only to the tissue in a right circular cylinder, coaxial with the capillary of length l and radius $d/2$, within which cylinder we are neglecting the effect of other capillaries than the one in question. The tissue we assume to be homogeneous and isotropic. The oxygen consumption, $-q$, we assume to be the same at all points in the region of supply of the capillary we are discussing. We are letting the z-axis be parallel to the capillary, with $z = 0$ at the arteriole and $z = l$ at the venule. The concentration, $c_o(z)$, of dissolved O_2 in the capillary, is assumed to be constant over any cross section, and to vary linearly with z from c_1 to c_2; similarly, the concentration, $x_o(z)$ of oxygen in hemoglobin, is assumed to vary linearly with z from x_1 at $z = 0$ to x_2 at $z = l$. Finally the external radial concentration gradient is assumed constant over any plane through the region of supply and perpendicular to the z-axis. We neglect any flow of O_2 parallel to the z-axis in the tissue. We denote by $c'(z)$ the concentration of O_2 in the tissue immediately outside the capillary wall, while $\bar{c}''$ is the concentration at $r = d/4$, $z = l/2$, which we shall call the "average" concentration in the tissue. r here is the radius vector in cylindrical coordinates, measured from the axis of the capillary.

There are three relations, equations (1), (2) and (3) below, which are immediately suggested. First, the total efflux of oxygen from the capillary per second may be expressed in terms of arteriolar and venular oxygen content of the blood:

$$\text{efflux per sec.} = \pi\, v\, r_0^2 (c_1 - c_2 + x_1 - x_2).$$

This quantity must be equal to the total oxygen consumption per second in the region of supply, since we are dealing with a steady state:

$$\pi\, v\, r_0^2 (c_1 - c_2 + x_1 - x_2) = -\pi\, q\, l \left[\left(\frac{d}{2}\right)^2 - r_0^2\right]. \qquad (1)$$

A second relation arises from the fact that the efflux per second through a small element of the capillary wall between z and $z + dz$ may be expressed in terms of the permeability of the capillary wall and the internal and external concentrations of dissolved O_2:

$$\text{efflux per sec. through } dz = h[c_0(z) - c'(z)] \cdot 2\pi r_0\, dz.$$

This may be set equal to the difference in total oxygen content of the blood before and after passing through dz:

$$2\pi r_0 h[c_0(z) - c'(z)]\, dz = -\left[\frac{dc_0(z)}{dz} + \frac{dx_0(z)}{dz}\right] \cdot v \cdot \pi r_0^2\, dz$$

or

$$2h\,[c_0(z) - c'(z)] = -\left[\frac{dc_0(z)}{dz} + \frac{dx_0(z)}{dz}\right] \cdot v r_0. \qquad (2)$$

Since we are assuming that $c_0(z)$ and $c'(z)$ vary linearly between the arteriole and the venule,

$$\frac{dc_0(z)}{dz} = \frac{c_2 - c_1}{l}$$

$$\frac{dx_0(z)}{dz} = \frac{x_2 - x_1}{l}.$$

Also,

$$c_0(z) = c_1 - \frac{(c_1 - c_2)z}{l}.$$

Using these values and the result of (1), we obtain an expression for $c'(z)$, the concentration of dissolved O_2 immediately outside the capillary:

$$c'(z) = c_1 + \frac{qz\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{v r_0^2} + \frac{z}{l}(x_1 - x_2) + \frac{q\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{2 r_0 h}.$$

Now we set up our third relation, which will lead us to an expression for $\bar{c}''$, the average O_2 concentration in the external tissue. First, we shall call $\bar{c}'$ the average value of $c'(z)$, which will exist at $z = l/2$:

$$\bar{c}' = c_1 + \frac{ql\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{2vr_0^2} + \tfrac{1}{2}(x_1 - x_2) + \frac{q\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{2r_0 h}.$$

Since we assume a linear fall of oxygen concentration along any radius vector, the radial gradient of concentration in the plane $z = l/2$ will be given by

$$-\frac{\bar{c}' - \bar{c}''}{d/4} = -\frac{\bar{c}' - \bar{c}''}{R}$$

where $R = d/4$. Hence the total flow outward through the surface of the cylinder of length l and radius R may be approximated by

$$\frac{2\pi R\, l(\bar{c}' - \bar{c}'')D}{R} = 2\pi l\, D(\bar{c}' - \bar{c}'').$$

Obviously this quantity is equal to the total flow outward through the capillary wall, *minus* the amount consumed in the cylinder:

$$2\pi l\, D(\bar{c}' - \bar{c}'') = \pi r_0^2 v(c_1 - c_2 + x_1 - x_2) - [-q\pi l(R^2 - r_0^2)]$$

or

$$\bar{c}' - \bar{c}'' = \frac{r_0^2 v(c_1 - c_2 + x_1 - x_2)}{2lD} + \frac{q(R^2 - r_0^2)}{2D}. \qquad (3)$$

On using values obtained above for $c_1 - c_2 + x_1 - x_2$ and $\bar{c}'$, and collecting terms, we obtain

$$\bar{c}'' = c_1 + \tfrac{1}{2}(x_1 - x_2) + q(4R^2 - r_0^2)\left(\frac{1}{2r_0 h} + \frac{l}{2vr_0^2}\right) + \frac{3qR^2}{2D}.$$

This expression is seen to be reasonable, since $\bar{c}''$ is an increasing function of r_o, h, q (the "rate of production" of oxygen in the tissue; $q < 0$), D, v, and $x_1 - x_2$; it is a decreasing function of l and d.

Although we have what seems a qualitatively reasonable expression for $\bar{c}''$, it remains to analyze our initial assumptions in order to investigate the possibility of a more exact and general approach to the problem.

The first assumption that appears to need refining is that of linear change in $c_o(z)$ along the capillary. It can be seen that, if there were no hemoglobin, all the oxygen being in solution, the concentration $c_o(z)$ would fall exponentially, since, roughly, the rate of fall of $c_o(z)$ would be proportional to $c_o(z)$ at any z.

The effect of the hemoglobin will, to first approximation, be to hold $c_o(z)$ nearly constant over quite a wide range of values of total oxygen $x_o(z) + c_o(z)$; this is due to the fact that the hemoglobin contains many times as much oxygen as does the plasma.

However, this approximation will be vitiated by at least two complicating factors. The first of these is the fact that the equilibrium constant of the dissociation of oxyhemoglobin is not fixed; the reaction is pushed in the direction of dissociation by the presence of free carbonic acid. The second complication is the time lag in the dissociation, which will prevent the existence of an equilibrium at any point along the capillary. These two effects will tend to neutralize each other, but just what the final result will be is not known at present.

Another assumption which will have to be altered is that of constant radial gradient of external concentration. Poisson's equation shows us that this gradient can never be constant in consuming tissue, and we intuitively feel that concentration ought to fall asymptotically to zero as r, the radius vector in cylindrical coordinates, increases.

In order to arrive at a more exact idea of the nature of the external gradient, we must first have consumption, $-q$, as a function of concentration, c. N. Rashevsky (1940) gives the following relation for oxygen consumption (the notation has been changed):

$$c = \alpha y + \frac{\beta y}{1 - y} \tag{4}$$

where

$c = O_2$ concentration outside a cell

α, β are constants

$y = q/q^*$, where $-q^* =$ limiting consumption for $c = \infty$.

If we solve Poisson's or an equivalent equation for c, having first substituted for $-q$ its value as given by equation (4), we should get an exact expression for oxygen concentration as a point function in consuming tissue.

Finally, it will be well to discuss another of the concepts employed in our approximate derivation of $\bar{c}''$. This is the concept of a "region of supply". In our approximation we assumed that the capillary in question supplied all the oxygen consumed in a region assumed to be cylindrical; we neglected the effect on concentration in this region of all other capillaries than the one under investigation. Although it is true that, if there are n capillaries supplying a volume V of tissue, the average capillary may be assumed to supply a volume V/n, and although it is further true that through any closed surface S constructed around any such volume V/n containing one capillary the net diffusion is zero, it is not true that the capillaries outside S have no effect on concentration inside S. It is obvious, for instance, that if one of the external capillaries stops flowing, S will, on the average, have to expand to include the volume $V/n - 1$; hence, concentration within S will be reduced.

The problem of determining the exact effect of distant capillaries may be approached in either of two ways: by summing, or integrating, the effect of a single capillary over all the capillaries in the tissue, or by finding the total diffusion out through S of products of the capillary within S. This quantity will be equal in magnitude to the diffusion inward from all other capillaries, the average value of which diffusion will thus be determined.

In concluding, the writer wishes to express his appreciation of the very helpful assistance and counsel given him by Dr. A. S. Householder.

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NOTE ON A POSSIBLE APPLICATION OF SOME CONCEPTS OF TOPOLOGY TO ASYMMETRIC ORGANIZATION OF PROTOPLASM

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A suggestion is made for the possible use of topology in the theory of asymmetric constituents of protoplasm.

At the present time we are not provided with the exact knowledge of the molecular skeleton of living matter, which could be placed at the bottom of any elaborate mathematical theory of structure and activity of living systems. The only starting point in our possession is presented by observations on optical activity of living matter. It appears reasonable in this connection to use some concepts of a specialized branch of mathematics, namely topology, in order to extract from the empirical records concerning optical activity of protoplasm some more general information concerning the properties of space in living systems. Topology is the science of general properties of space, and some of its generalizations have repeatedly been found useful in all those fields of natural knowledge that deal with the properties of complex spatial figures.

The empirical data of biology show that the molecules of various substances participating in the fundamental metabolic processes always possess the same (left) steric configuration (for a summary see Gause, 1941). It is only in leaving these fundamental processes that the organic molecules can sometimes change their configuration into an inverse, the right one. Such an inversion of configuration is often observed in pigments, excretory and some other secondary substances. In other words, the primary physiological processes involve molecules of the same left orientation. These molecules form an *equioriented manifold,* in the topological sense. However, the equiorientation does not extend upon all the manifolds of molecules in living systems, but is restricted to primary constituents only. In the secondary substances, dissociated from the primary complex, the equiorientation does no longer exist.

The equiorientation of a manifold belongs to one of the basic concepts of topology. All the manifolds of three-dimensional figures (molecules included) are divided by topology into two categories: first, the *orientable* ones, which can be oriented throughout in a single specific manner (equiorientated); and, second, the *non-orientable* ones, which cannot be oriented in the sense just given.

In this way from the view point of topology the diversities between the primary and secondary constituents of living matter are very profound, as far as these belong to two different categories of topological structures. The primary constituents can be characterized as the orientable manifolds, whereas the secondary constituents represent non-orientable manifolds.

Having now passed from biological to topological language, we can analyze a little further the diversities between the orientable and non-orientable manifolds of molecules. In the equioriented manifold subject to various transformations any inversion of orientation of a component figure is excluded. Topology teaches us that such an exclusion requires some special conditions. It is required that such transformations should be "forbidden" which by purely geometric reasons inevitably lead to an inversion of orientation of a figure. A relatively simple geometric example of such a "forbidden" operation of inversion is provided by the so-called Möbius band (Seifert and Threlfall, 1934). When a circle rotating clockwise is passed through such a band and then placed against its previous image, it will now be found rotating in a counter-clockwise direction.

In other words, the equiorientation of the manifold of molecules in primary constituents of protoplasm is attained by means of forbidding some specific intermediate topological transformations of these molecules. Such a forbidding is not operative for the secondary constituents of protoplasm.

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STATISTICAL DISTRIBUTION OF IMPEDANCE ELEMENTS IN BIOLOGICAL SYSTEMS

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Electric impedance measurements on systems consisting of non-uniform elements (e.g. nerve bundles, cell suspensions, imperfect dielectrics) can be interpreted if the impedance characteristics of the individuals and their impedance distribution are known. Conversely, given the observed overall impedance, $z(p)$, the impedance distribution of the individuals is not uniquely determined in both phase angle and static capacitance. If all individual phase angles are equal, the distribution, $D(\tau)$, is the solution of Stieltjes' integral equation

$$F[z(p)] = \int_0^\infty \frac{D(\tau)\,d\tau}{1+p\tau},$$

F being a known function of the geometry of the system. It is shown that the phase angle of the equivalent suspension approaches that of the original suspension as the dispersion of $D(\tau)$ decreases.

The majority of impedance measurements on biological materials, have, until quite recently, (Cole and Curtis, 1938b) been made on multifibered preparations (e.g., nerve or muscle), or multicellular suspensions (e.g., marine eggs or erythrocytes) (Cole and Curtis, 1936; hereinafter abbreviated C 1936). In general, the aim of such measurements has been to determine the impedance characteristics of the individual units comprising the system from the overall results found for the entire population. In the case of certain marine eggs (*Hipponoë* and *Arbacia*, e.g.) where the population is nearly uniform, Maxwell's calculations for the impedance of suspensions of spheres have given results which are entirely consistent with impedance measurements on single eggs. On the other hand, nerve and muscle, which consist of parallel fibers showing wide variation in diameters, membrane capacities, and phase angles, give rise to overall "polarization" impedance characteristics which do not agree, insofar as the comparison has been made, with experiments on individual axons. The suggestion has been made (C 1936) that the appearance of polarization impedances in biological materials may be attributable entirely to the statistical variation of the electrical parameters (other than phase angle) of the individuals of the population. This interpretation is not completely adequate in the only case which has been investigated, viz., the fin nerve of the squid; for, as Curtis and Cole have pointed out, (1938b) individual giant axons exhibit a polarization impedance with an average phase angle of about 76°, whereas the phase angle for an equivalent uniform nerve lies between 40° and 50°. It thus appears that the observed polarization impedance in biological systems is partly due to polarization impedance of the individual members, and partly due to a statistical distribution of sizes, static capacitances, and phase angles in the preparation.

The statistical distribution of the individuals in a system whose overall impedance characteristics are known, is related to the impedance of the equivalent homogeneous system by an integral equation, which, in certain simple cases, reduces to an equation recently discussed by R. Fuoss and J. Kirkwood (1941) in connection with the distribution of relaxation times in imperfect dielectrics. However, since the integral equation is an instance of one treated by Stieltjes in connection with his moment problem, it may be of some mathematical interest to present an alternative solution as an application of the Stieltjes theory (Perron, 1929).

The Distribution Problem

The present considerations will be confined to the case mentioned in C 1936: the impedance of a statistical distribution of parallel cylinders, although the final results are applicable to spheres with very little change. Let us suppose that the system consists of three phase (external, membrane, internal) parallel cylinders each of whose membranes has specific impedance $\bar{z}(i\,\omega)^{-m}$, where $\omega/(2\pi)$ is the frequency of the measuring E.M.F., $m\,\pi/2$ is the membrane phase angle, and $i = \sqrt{-1}$. Then by a simple extension of some considerations in C 1936, the specific impedance, z, of the group of fibers whose volume concentration, $G(\bar{z}, m)$, lies between $G(\bar{z}, m)$ and $G(\bar{z} + d\bar{z}, m + dm)$, is determined by

$$d\left(\frac{z - r_1}{z + r_1}\right) = G(\bar{z}, m)\,\frac{r_2 - r_1 + \bar{z}(i\,\omega)^{-m}}{r_2 + r_1 + \bar{z}(i\,\omega)^{-m}}\,d\bar{z}dm, \tag{1}$$

where r_2 and r_1 are the specific internal and external resistances, respectively, and G is normalized so that

$$\int_0^\infty \int_0^1 G(\bar{z}, m)\;dmd\bar{z} = G_0, \tag{2}$$

G_0 being the volume concentration of the equivalent uniform suspension. The specific impedance, Z, of an equivalent *homogeneous* suspension is given by

$$\frac{Z-r_1}{Z+r_1}=G_0\frac{r_2-r_1+z_3}{r_2+r_1+z_3}, \tag{3}$$

where z_3 is the equivalent membrane specific impedance. If we equate the right member of (3) and the integrated right side of (1), we find, after subtracting G_0 from each side,

$$\frac{1}{1+z_3/W}=\int_0^\infty\int_0^1\frac{G(z,m)\,dm d\bar{z}}{G_0[1+\bar{z}(i\,\omega)^{-m}/W]}\,, \tag{4}$$

where $W=r_1+r_2$.

The function $z_3(\omega)$ is known empirically to have the form $\bar{z}_3(i\,\omega)^{-\beta}$, $\bar{z}_3$ and β being constants. However, it is easy to show that, in general, (4) does not determine $G(\bar{z}, m)$ uniquely. For, suppose the distribution in $\bar{z}$ and the distribution in m are uncorrelated. Then (Kenney, 1939, p. 64) $G(\bar{z}, m)$ must be expressible as the product of two functions, $h(\bar{z})g(m)$. Substituting this product for $G(\bar{z}, m)$ in (4), and integrating with respect to m, we find

$$\frac{1}{1+z_3(i\,\omega)^{-\beta}/W}=\int_0^\infty K(\omega,\bar{z})\,h(\bar{z})\,d\bar{z}\,, \tag{5}$$

where the kernel, $K(\omega,\bar{z})$, is defined by

$$K(\omega,\bar{z})=\int_0^1\frac{g(m)\,dm}{G_0[1+\bar{z}(i\,\omega)^{-m}/W]}. \tag{6}$$

Since the solution, $h(\bar{z})$, of the integral equation (5) depends on $K(\omega,\bar{z})$, which in turn depends on $g(m)$, we can choose $g(m)$ arbitrarily and get a different $h(\bar{z})$ for each admissible choice. This means that data on $z_3(\omega)$ alone will not determine $G(\bar{z}, m)$; it is also necessary to know the distribution in one of the variables, $\bar{z}$ or m, in order to find the distribution in the other.

In the absence of any data on $g(m)$, we shall make the simplest assumption (which is certainly incorrect for nerve, but is probably correct for marine eggs), viz., $g(m)=\delta(m-m_0)$ where δ is the Dirac delta function. In this case equation (5) may be reduced to a canonical form

$$\frac{1}{1+p^a}=\int_0^\infty\frac{D(\tau)\,d\tau}{1+p\tau}, \tag{7}$$

where

$$\begin{aligned} \alpha &= \beta / m_0 , \\ p &= (i\,\omega)^{-m_0} (z_3/W)^{1/a}, \\ \tau &= W^{(1/a-1)} \bar{z} / \bar{z}_3^{\,1/a}, \\ D(\tau) &\equiv (1/G_0) \bar{z}_3^{\,1/a} W^{(1-1/a)} h(\tau). \end{aligned} \tag{8}$$

The physical significance of the distribution variable $\bar{z}$ depends on the impedance characteristics of the individual membranes. Thus, for elements whose membranes are pure static capacitances, $\bar{z} = (C_M a)^{-1}$ and $m_0 = 1$, where C_M is the membrane capacitance per unit area and a is the fiber radius. If, furthermore, the specific properties of the fibers are all alike so that C_M is the same for all fibers, the distribution will be a simple size distribution. However, the assumption $m_0 = 1$ and $\bar{z} = (C_M a)^{-1}$ is somewhat irrelevant for nerve fibers in the light of Cole and Curtis' single fiber measurements; it seems to be justified only in the case of marine egg suspensions (Cole and Curtis, 1938a).

Solution

The substitutions

$$\phi(\tau) = \int_0^{\tau} D(\tau)\, d\tau , \qquad p = 1/\zeta , \tag{9}$$

reduce (4) to

$$\frac{\zeta^{a-1}}{1+\zeta^a} = \int_0^{\infty} \frac{d\,\phi(\tau)}{\zeta + \tau}, \tag{10}$$

which is the form associated with Stieltjes' moment problem. We employ Stieltjes' method of solution as given by Perron (1929, p. 372).

This solution $\phi(\xi)$, where continuous, is given by

$$\phi(\xi) - \phi(0) = \lim_{\eta = +0} R \left(\frac{-1}{\pi\, i} \int_{-\xi + i\eta}^{+i\eta} \frac{\zeta^{a-1}\, d\,\zeta}{1 + \zeta^a} \right), \tag{11}$$

where the value of the function R is the real part of its argument; from (11), this is $-1/\pi$ times the coefficient of i in the definite integral. For any $\eta \neq 0$ the integral has the value

$$\frac{1}{\alpha} \log\,(1 + \zeta^a) \Bigg|_{-\xi + i\eta}^{+i\eta} = \frac{1}{\alpha} \log \frac{1 + (+\,i\,\eta)^a}{1 + (-\xi + \mathrm{i}\,\eta)^a}, \tag{12}$$

and the limit of the imaginary part of this logarithm as η approaches zero from the positive side is needed for (7). Since the argument of the logarithm can be written as

$$P e^{i(\theta_1 - \theta_2)}$$

where P is real and θ_1 and θ_2 are the amplitudes of the numerator and denominator, respectively, of the fraction, our limit becomes, upon taking logarithms,

$$\lim_{\eta=+0} \frac{-1}{\pi\alpha}(\theta_1 - \theta_2) .$$

The values of θ_1 and θ_2 are, from (9),

$$\begin{aligned} \theta_1 &= \arctan \frac{\eta^a \sin \alpha\pi/2}{1 + \eta^a \cos \alpha\pi/2}, \\ \theta_2 &= \arctan \frac{\rho^a \sin \alpha\theta}{1 + \rho^a \cos \alpha\theta}, \end{aligned} \tag{13}$$

where

$$\rho^2 = \xi^2 + \eta^2, \qquad \tan\theta = -\eta/\xi \tag{14}$$

and θ lies in the second quadrant. The quantities η^a and ρ^a are positive and real.

As η approaches zero, $\tan\theta_1$ approaches zero, and hence θ_1 approaches zero or some integral multiple of π. We may, however, ignore additive constants [absorbing these into $\phi(0)$], and regard the limit of θ_1 as zero. The angle θ has the limit π, and ρ^a the limit ξ^a, whence

$$\lim_{\eta=+0} \theta_2 = \arctan \frac{\xi^a \sin \alpha\pi}{1 + \xi^a \cos \alpha\pi},$$

and therefore, where ϕ is continuous [cf. equation (11)],

$$\phi(\xi) = \phi(0) + \frac{1}{\pi\alpha} \arctan \frac{\xi^a \sin \alpha\pi}{1 + \xi^a \cos \alpha\pi} . \tag{15}$$

In case $\alpha = 1$, the arc tangent has the value zero or an integral multiple of π; this implies that $\phi(\xi)$ is constant except at points of discontinuity. The original equation (10) becomes

$$\frac{1}{1+\zeta} = \int_0^\infty \frac{d\,\phi(\tau)}{\zeta + \tau}, \tag{16}$$

and if the discontinuities of ϕ occur at the points τ_i, then the integral has the value

$$\int_0^\infty \frac{d\,\phi(\tau)}{\zeta+\tau} = \Sigma \frac{\phi(\tau_i + 0) - \phi(\tau_i - 0)}{\zeta + \tau_i} .$$

This will equal the left side of (16) if and only if there is a single discontinuity at $\tau = 1$, with

$$\phi(1+0) - \phi(1-0) = 1 . \tag{17}$$

If $\phi(0) = 0$, then (cf. Fig. 1)

$$\begin{aligned} \phi(\xi) &= 0 , \qquad 0 \leq \xi < 1 , \\ \phi(\xi) &= 1 , \qquad 1 < \xi . \end{aligned} \tag{18}$$

Thus $D(\tau)$, which is the derivative of $\phi(\tau)$, is zero everywhere except at $\tau = 1$, where it becomes infinite. The function $D(\tau)$ in this case is identical with Dirac's δ-function.

The physical significance of the discontinuous integrated distribution for $\alpha = 1$ is the following. If the phase angle of the individual elements is the same as the phase angle of the equivalent suspension $(\beta = m_0)$, so that $\alpha = 1$, then, by the previous paragraph, the standard deviation of the distribution is zero. This is fairly well verified in the case of the marine eggs. Cole and Curtis (1938a) find phase angles in single marine eggs corresponding to values of m very near 1, while suspensions of marine eggs in which "the standard deviation of cell diameter is of the order of one per cent . . . give a value of $\beta = 1.0$ within experimental error" (C 1936).

For $0 < \alpha < 1$, we obtain $D(\tau)$ by differentiating (15) (the assumption that $\phi(\xi)$ is continuous being justified on physical grounds):

$$D(\tau) = \frac{1}{\pi} \frac{\tau^{\alpha-1} \sin \alpha \pi}{\tau^{2\alpha} + 2\,\tau^{\alpha} \cos \alpha \pi + 1}, \tag{19}$$

and this is the required distribution. The validity of this formula in the special case $\alpha = 1/2$ is readily checked by direct integration of (7).

The distribution (19) is most conveniently visualized by making the substitution $s = \log \tau$. Then the logarithmic distribution function, $F(s)$, defined by

$$F(s)\,ds = D[\tau(s)]\; d\,\tau(s)$$

is, from (19),

$$F(s) = \frac{1}{2\pi} \frac{\sin \alpha \pi}{\cosh \alpha s + \cos \alpha \pi},$$

which is exactly the distribution obtained by Cole and Cole (1941). Graphs of $\phi(\tau)$, $D(\tau)$, and $F(s)$ for several values of α between 0 and 1, are given in the accompanying figure. It will be noticed that as α approaches unity, the dispersion of the distribution decreases; i.e., as the uniformity of the suspension increases, the phase angle of its members approaches that of the equivalent homogeneous suspension.

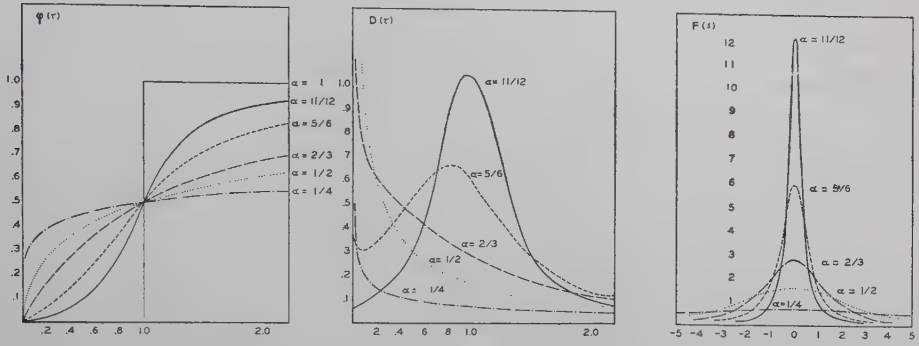

FIGURE 1

This result is intuitive, since the more uniform a suspension, the more it resembles its equivalent homogeneous suspension.

The writers wish to thank Professor H. S. Wall of Northwestern University for having pointed out to them Perron's treatment of the Stieltjes problem. It is to a remark made by Professor Wall in a lecture on continued fractions (1941), and to a comment by Professor K. S. Cole that the origin of this paper is due.

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A THEORY OF STEADY-STATE ACTIVITY IN NERVE-FIBER NETWORKS III: THE SIMPLE CIRCUIT IN COMPLETE ACTIVITY

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Continuing the investigation previously introduced, it is shown here that when the product of the activity parameters of the circuit is not exceeded by unity (algebraically) a steady state is not possible in which all fibers of the circuit are active, whereas when this product is exceeded by unity, any stimulus pattern which is consistent with such a state of complete activity is inconsistent with any state of partial activity of the circuit.

In two previous papers (Householder, 1941; these will be denoted by I and II) the general problem of the nature of the steady-state activity in a network of neurons was introduced. The case of a constant stimulus only was considered, and it was assumed that a single fiber, when acted upon by a constant stimulus which exceeds a certain threshold, will then react with an intensity which is asymptotically proportional to the amount by which the constant stimulus exceeds this threshold. The threshold and the constant of proportionality, which was called the "activity parameter," are characteristic of a given fiber. Under these assumptions, the case of a simple circuit of n fibers was discussed, and it was shown that to prescribe the intensities of the stimuli which are applied from without to the several fibers does not suffice in all cases to determine which of the fibers of the circuit will respond, in case there are inhibitory fibers present. The results were, however, incomplete, inasmuch as it was assumed that there was always at least one fiber of the circuit which was inactive. It is the purpose of this note to supplement these results by removing this restriction.

The notation and terminology is the same as that employed in I and II, and will not be defined again here. Let

$$\Delta = 1 - a_1 a_2 \cdots a_n , \tag{1}$$

where the a_i are the activity parameters of the fibers of the circuit. Subject to the restrictions mentioned, it was found previously that when $\Delta > 0$, and also when the circuit consists of excitatory fibers only (every $a_i > 0$), then the external stimuli ("stimulus pattern") do determine uniquely the activity of the entire circuit and its amount for each fiber (the activity pattern and the excitation pattern, respectively), whereas in the contrary case, there always exists a stimulus pattern with which each of two distinct activity patterns is consistent. Here we shall show first that *when $\Delta \leq 0$ it is not possible for all the fibers to be acting at once in a steady state,* and second that *when $\Delta > 0$, no stimulus pattern which is consistent with a state of complete activity can be also consistent with a steady state in which only some, but not all of the fibers are acting.*

The first result in the case all $a_i > 0$ has already been obtained in I, and simply means that for large stimuli and for such circuits, the activity parameter must be regarded as variable, the assumption of constancy being an inadequate approximation to the true situation. Where inhibitory fibers are present, however, the equations indicate that as the stimuli are increased, whichever inhibitory fiber becomes active first, this one will tend to dominate the circuit and render succeeding fibers inactive, so that in no case (when $\Delta \leq 0$) is it possible for all fibers to act simultaneously. To see this, consider any $SP\sigma$ which is supposed to be such that a steady state of complete activity can result. Then there must exist some mode of gradual application of these stimuli, perhaps a little at a time to one and then another of the synapses, until all fibers are active. In fact, it should be possible to do this slowly, no increment being made to the stimulus at any synapse until the steady state has been reached as a result of the preceding ones. Then at some stage, all fibers but one can be made active, and the final increment will be applied to this fiber to render it active, after which all fibers will be acting. But, the final step will therefore be to make $\sigma_i^{(n)}$ positive where it was previously negative or zero (i being the number of the fiber). But if this is done, and if all fibers thereby become active, then in the steady state the resulting values of the y_i at the several synapses are the solutions of equations (7) of I, where every $\alpha_i = a_i$, and this solution is

$$y_i = \sigma_i^{(n)}/\Delta\,, \tag{2}$$

as given in (13) of I. But $\sigma_i^{(n)} > 0$, $\Delta \leq 0$ by hypothesis, wherefore $y_i < 0$ (or else $y_i = \infty$), whence the fiber i cannot remain in activity if all the other fibers remain active. Thus, putting fiber (i) into activity necessarily stops at least one of the other, hitherto acting fibers.

Now suppose $\Delta > 0$ so that it is possible to have a steady state of complete activity, and let σ be an SP with which this state of complete activity is consistent. The AP is defined by $\alpha_i = a_i$ and the EP is defined by the y_i given in (2). Let this same $SP\sigma$ be consistent with some AP $\beta \neq \alpha$, i.e. an AP which has at least one zero. Let the corresponding EP be z_i. Let the zeroes of β be located at $i_1, i_2, \cdots, i_p$ where

$$1 \leq i_1 < i_2 < \cdots < i_p \leq n . \tag{3}$$

Let

$$i_p + \omega_1 = n + i_1 , \qquad i_1 + \omega_2 = i_2 , \cdots , \qquad i_{p-1} + \omega_p = i_p . \tag{4}$$

Also let

$$\begin{aligned} A_{i,\, j+1} &= a_i\, a_{i+1} \cdots a_j && \text{when} \quad i < j \leq n , \\ A_{i,\, j+1} &= a_i\, a_{i+1} \cdots a_n a_1 \cdots a_j && \text{when} \quad j < i \leq n . \end{aligned} \tag{5}$$

Then if h does not coincide with any of the i_r, we have

$$y_{h+1} = \sigma_{h+1} + a_h y_h \qquad z_{h+1} = \sigma_{h+1} + a_h z_h ,$$

whence

$$y_{h+1} - z_{h+1} = a_h (y_h - z_h) ,$$

and by induction

$$y_{h+j} - z_{h+j} = A_{h,\, h+j} (y_h - z_h) , \tag{6}$$

provided the sequence $h, h+1, \cdots, h+j-1$ does not include any of the i_r. On the other hand, if $\beta_h = 0$, while the sequence $h+1, \cdots, h+j-1$ does not include any other i_r, then z_h must be omitted from equation (6) and we have

$$y_{h+j} - z_{h+j} = A_{h,h+j}\, y_h . \tag{7}$$

These equations are not restricted to the case when every $\alpha_i \neq 0$, but are more general. In fact we have the

LEMMA. *If* σ_i *is an* SP *consistent with an* AP α; *if* τ_i *is an* SP *consistent with an* AP β; *if*

$$\alpha_{h+1}\, \alpha_{h+2} \cdots \alpha_{h+j-1}\, \beta_{h+1}\, \beta_{h+2} \cdots \beta_{h+j-1} \neq 0 ;$$

and if

$$\sigma_{h+1} = \tau_{h+1} , \cdots , \sigma_{h+j-1} = \tau_{h+j-1} ,$$

then equation (6) *holds provided also* $\alpha_h \beta_h \neq 0$, *but* (7) *holds when* $\beta_h = 0$.

If, now, we set $h = i_r$, and $j = \omega_{r+1}$, then we have from (7) that

$$y_{i_{r+1}} - z_{i_{r+1}} = A_{i_r, i_{r+1}}\, y_{i_r} . \tag{8}$$

Since $y_{i_{r+1}} > 0$, $z_{i_{r+1}} \leq 0$, $y_{i_r} > 0$, it follows from (8) that

$$A_{i_r,i_{r+1}} > 0\,. \tag{9}$$

The equations (8) also imply the inequalities

$$y_{i_{r+1}} \le A_{i_r,i_{r+1}}\, y_{i_r} \tag{10}$$

and from this system of p inequalities we easily obtain

$$y_{i_r} \le A_{1,n+1}\, y_{i_r}\,,$$

and therefore

$$\Delta \le 0\,,$$

contrary to hypothesis.

It follows, therefore, that when $\Delta > 0$, every state of partial or complete activity of the circuit is possible and is uniquely determined by the applied stimulus pattern, whereas for $\Delta \le 0$ a steady state of complete activity is never possible. Consequently the restriction which was repeatedly imposed in II, that each *AP* considered shall have at least one zero, was either unnecessary (when $\Delta > 0$) or automatically fulfilled (when $\Delta \le 0$).

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THEORY OF THE DISTRIBUTION OF RESPONSE TIMES IN NERVE FIBERS

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On the basis of Rashevsky's nerve excitation equations, an expression is derived for the distribution of response times attributing the variation to the fluctuations in threshold. The resulting equation is compared with available data and agreement is found.

The suggestion has been made that the variation in response times of a nerve fiber is due to the fluctuations of threshold (E. A. Blair and J. Erlanger, 1933, 1936; C. Pecher, 1939). A discussion of possible sources of the threshold variations is given by C. Pecher (1939). Of particular interest is the suggestion that the principal source of the fluctuations is the variation in the fiber as would be expected from the kinetic theory. Calculations showed this to be very plausible. Various experiments showed that the fluctuations were random, and the fluctuations in two adjacent fibers were independent.

It was shown by H. Jasper and T. Perkins (1932), that for nerve muscle preparations the cumulative response curve plotted against time could be closely approximated by an ogive. This would imply that the derivative curve, or the curve of the distribution of response with time, would be a normal curve. However, this is not quite so. It is the purpose here to derive this relation more exactly and on the basis of equations which have considerable experimental support.

Let us assume that the variation in response times is due entirely to the variation in threshold and using N. Rashevsky's form of the two-factor excitation theory (Rashevsky, 1938, chap. xvii), derive the expression for the distribution of response times. If the variations in threshold were due to fluctuations in ion concentrations as suggested, the latter would be randomly distributed, and since the numbers are fairly large, one obtains for the distribution of the threshold, the well known error curve. It is assumed in the derivation that the numbers dealt with are large, which they are, and that the variations are small compared with the average value. In terms of the threshold distribution this means that the standard error must be small compared to the mean threshold. But, this is true for the nerve as C. Pecher (1939) obtains, for the ratio, values of about one or two per cent. Thus, we may assume a normal error curve.

For constant current excitation, N. Rashevsky's equations are (Rashevsky, 1938, p. 164)

$$\varepsilon = \varepsilon_0 + \frac{KI}{k}(1 - e^{-kt}), \tag{1}$$

$$j = j_0 + \frac{MI}{m}(1 - e^{-mt}), \tag{2}$$

where the condition for excitation is $\varepsilon \geq j$. The time t is measured from the application of the stimulating current I.

Let

$$\frac{K}{k} = \frac{M}{m} \tag{3}$$

so that there is normal accommodation, (Hill, 1935). Then

$$\varepsilon - j = -(j_0 - \varepsilon_0) + \frac{KI}{k}(e^{-mt} - e^{-kt}). \tag{4}$$

The value of ε_0 and j_0, or actually their difference, is considered to be constant. But let us now consider that at any particular instant it may have some value $\varepsilon_0 - j_0 - \xi$ so that $\varepsilon_0 - j_0$ is the average value and ξ is a fluctuation from the average. Then, instead of (4) we have

$$\varepsilon - j = -(j_0 - \varepsilon_0) + \frac{KI}{k}(e^{-mt} - e^{-kt}) - \xi. \tag{5}$$

If $p(\xi)\, d\xi$ is the probability that ξ has a value between ξ and $\xi + d\xi$, then as ξ is normally distributed,

$$p(\xi) = \frac{1}{\sqrt{2\pi}\,\sigma} e^{-\frac{\xi^2}{2\sigma^2}}, \tag{6}$$

where σ is the standard deviation and equals to 1.67 times the probable error. The condition for excitation to take place is $\varepsilon \geq j$, or because of (5) we may also write for the condition that excitation occur,

$$\xi \leq \frac{KI}{k}(e^{-mt} - e^{-kt}) - (j_0 - \varepsilon_0). \tag{7}$$

If we define $P(I, t)$ as the probability that a response will occur for a fixed time t when the stimulus intensity is I, then by the definition of P and from equation (7),

$$P(I\,,t)=\int_{-\infty}^{\xi_1} p(\xi)\,d\,\xi\,, \tag{8}$$

where

$$\xi_1(I\,,t)=\frac{KI}{k}\,(e^{-mt}-e^{-kt})-(j_0-\varepsilon_0)\,. \tag{9}$$

If t is constant, then ξ_1 is linear with I. But because t is a function of I, ξ_1 in (9) is not linear with I. But if one recalls that for stimuli near the threshold (it is only these in which we are interested for the present) a response will not be apt to occur until ξ_1 is very nearly zero, that is, until it is a few per cent of the initial value $(j_0-\varepsilon_0)$.From the fact that the stimulus is near threshold, the factor $e^{-mt}-e^{-kt}$ of the expression (9) is near its maximum value and thus it is approximately a constant. Hence for values of I near the threshold (defined as that value of I for which the proportion of responses is one-half), ξ_1 is essentially independent of t. The unit in which the stimulus is expressed is immaterial as long as the threshold and standard deviation are measured in the same unit. Thus, defining

$$I'=\frac{KI}{k}\,(e^{-mt}-e^{-kt}) \tag{10}$$

$$I'_0=j_0-\varepsilon_0 \tag{11}$$

then equation (8) becomes

$$P'(I')=\int_{-\infty}^{I'-I'_0} p\,d\,\xi\,. \tag{12}$$

A comparison of this expression with data by C. Pecher on a single fiber from a frog sciatic, is shown in Figure 1, where the ex-

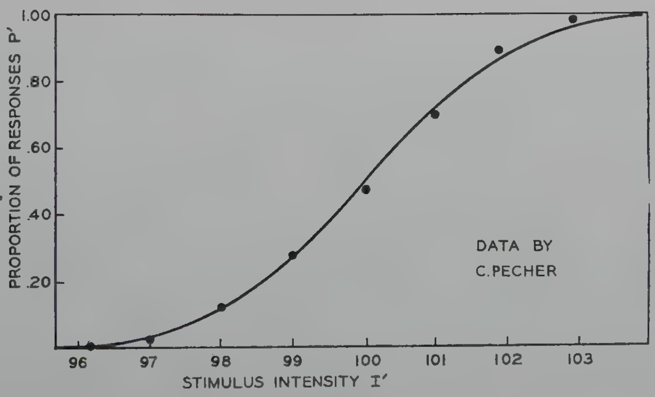

FIGURE 1

perimental values are solid circles, and the curve is that of equation (12) with $I'_0 = 100$, and $\sigma = 1.667$, or

$$P'(I') = \frac{.6}{\sqrt{2\pi}} \int_{-\infty}^{(I'-100)} e^{-.36\frac{\xi^2}{2}} d\xi . \tag{13}$$

The agreement further emphasizes the validity of the assumption of a normal distribution of ξ in equation (6).

We now proceed to the derivation of the expression for the distribution of response times for a constant I. If a fiber being stimulated by an intensity I, has not responded at a time t, the probability that a response will occur between t and $t + dt$ is given by Pdt where P is given by equation (8), and where $\xi_1(t)$ is given by equation (9). In order that a response should take place between t and $t + dt$, it is necessary that no response shall have occurred between zero and t (or for that matter for a sufficiently long time before $t = 0$, but no response occurs since I is then zero). Let the time from zero to t be divided into n equal intervals, Δt. If $q(I, t) \Delta t$ is the probabilty that a response occurs during the interval t to $t + \Delta t$, when the stimulus intensity is I, $q \Delta t$ is given by the product of the probabilities that no responses occur in the preceding intervals and the probability that response does occur in the interval t to $t + \Delta t$, or

$$q \Delta t = (1 - P_0 \Delta t)(1 - P_1 \Delta t) \cdots (1 - P_{n-1} \Delta t) P_n \Delta t , \tag{14}$$

where P_i is the probability $P(I, t_i) = P(I, i \Delta t)$ that a response will take place between t_i and $t_i + \Delta t = t_{i+1}$ if no response has occurred before t_i. Equation (14) may be written

$$\log q = \sum_{i=0}^{n-1} \log (1 - P_i \Delta t) + \log P \tag{15}$$

where q and P are taken at t. Since Δt may be taken as small as desired, we may expand each logarithmic term and use only the first term of the expansion in each case, or

$$\begin{aligned} \log q &= - \sum_{i=0}^{n-1} P_i \Delta t + \log P , \\ &= - \int_0^t P \, d\tau + \log P , \end{aligned} \tag{16}$$

so that

$$q(I, t) = P(I, t) e^{-\int_0^t P(I,\tau) d\tau} , \tag{17}$$

where $P(I, t)$ is given by equation (8) and $\xi_1(t)$ of the latter equation is given by equation (9) for any intensity of the stimulus I. From equation (17) we see that the mean response time must decrease as the intensity I increases, a fact which is well known. The spread in the response times must get smaller as the intensity is increased. This is shown in the experiments by C. Pecher (1939). Whether or not the agreement here is also quantitative remains to be seen.

We next inquire as to the relation between q and t. C. Pecher (1939) gives two such curves in which the intensity of stimulation is near threshold. As the exact value is not explicitly stated, it was assumed that the value in each case was exactly threshold and the area under the curves in each case reduced to one half. This led to the points shown plotted in Figure 2. Since the values of the probable errors relative to the threshold were not given, these were left to be found by trial and error in fitting the respective curves to equation (17). Similarly the values of k and m were not given, though the value of k can be obtained to a first approximation without difficulty. The ratio k/m has some value from 10-100 (Katz, 1939).

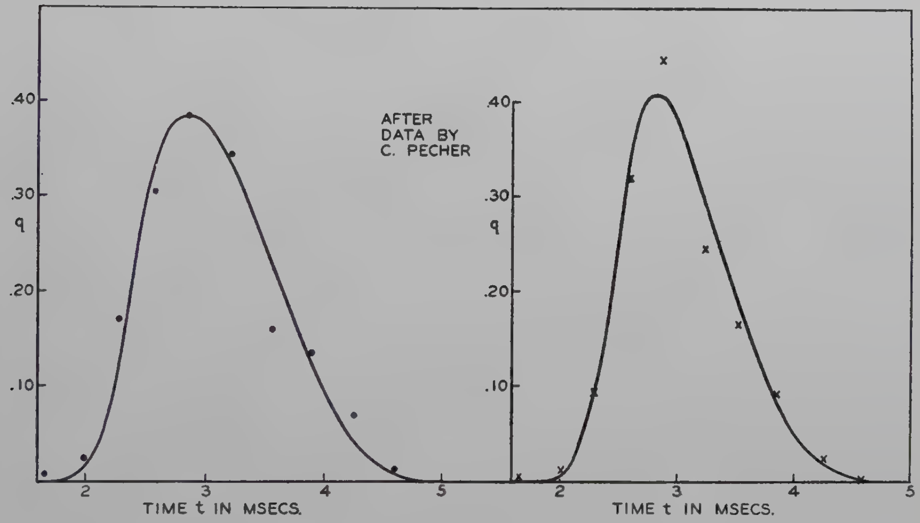

FIGURE 2

For the left curve, the following values were taken as parameters: the ratio of the standard deviation, σ, to the threshold (given by I in equation (9) for $\xi_1 = 0$ and such a value of t that $e^{-mt} - e^{-kt}$ is a maximum) was 2.16%, or 1.3% probable error; $k = .95$ msec., and $m = .0633$ msec. or $k/m = 15$; thus

$$\xi_1 = 130\ [.7692 + e^{-.95t} - e^{-.0633t}]\ .$$

For the right curve the following values of the parameters were used: the ratio of the standard deviation to threshold was .88%, or in terms of the probable error .53%: $k = 1.35$ msecs., $m = .027$ msec. or $k/m = 50$; or

$$\xi_1 = 105.4\,[.9048 + e^{-1.35t} - e^{-.027t}] \,.$$

The curves are not particularly sensitive with regard to m. A fairly large change in m, as from 1/5 k to 1/15 k showed no appreciable effect on the curve, except that in the former case σ had to be taken as 3.1% whereas in the latter $\sigma = 2.16\%$ in terms of the threshold. The former is a rather high value, the latter is about average (C. Pecher, 1939). Thus with the value of σ known, there remains not much variation possible for m. But as k and m can be independently determined, it is clear that in principle all the parameters in equation (17) can be determined independently, and with these given, one can plot the expected distribution. Whether or not the actual values agree is then readily tested. Under these conditions, agreement would strongly suggest that the variations in response times is due almost entirely to the variations in the threshold. With a knowledge of the latter and sufficient additional information, the distribution of response times is predicted quantitatively.

It is of interest to note that regardless of the value assumed for the per cent standard deviation no fit can be obtained if m is taken too small. In the first curve, a value of m equal to $k/50$ is already too small, in the second, $k/100$ is probably too small. Thus to obtain any agreement at all, it is essential that a two factor theory rather than a one factor theory be assumed. It has been suggested that the second factor does not occur under physiological conditions or if the fiber is amply perfused (Parrack, 1940). If so, we should expect the distribution of the response times under the latter conditions to show a slower fall for larger values of the response time. The experimental curve should be fit by equations (17), (8) and (9) where m is set equal to zero. In this case, it should be noted that the threshold as defined by $j_0 - \varepsilon_0$ is not equivalent to the definitions in terms of a fifty per cent response, and one cannot assume them to be approximately equal.

Perhaps it should be emphasized that the validity of equation (17) does not depend upon the initial equations in ε and j. If one is given the distribution of thresholds of a particular nerve under a set of conditions, and also the empirical excitatory state as a function of time, then the operations indicated by equation (17) lead one to the distribution of response times. No unknown parameters are involved. If the conditions were maintained constant throughout the experiments, agreement should be very significant, especially if various types of fibers were used and if the initial conditions were varied widely.

An expression for the distribution of response times for a single fiber has been obtained under the assumption that this variation is due only to the known variation in excitability. The predictions have been compared with available experimental data in which not all the required data were available. If the data were sufficient the resulting expression would contain no arbitrary parameter. In the cases tested, the values assumed for the parameters not given are consistent with other data. To the extent of this agreement, it would seem that the variation in the time required to set up an impulse is largely due to the known variations in threshold.

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APPLICATION OF THE GENERAL FLUID CIRCUIT THEORY TO THE CHLORIDE-BROMIDE-DEUTERIUM OXIDE EXPERIMENT

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The general fluid circuit theory of active chloride absorption is applied to an experiment in which chloride, bromide, and deuterium oxide were simultaneously absorbed from the lower ileum, chloride only moving against a concentration gradient. The conclusion is reached that the constant for active absorption of deuterium oxide is equal, within reasonable limits of error, to the constant for active chloride absorption in accordance with the assumption that the absorption of water carries chloride out of the intestinal lumen without changing its concentration.

The original simple form of the fluid circuit theory (Ingraham, Peters, and Visscher, 1938) assumes that the absorption of water at the rate R_o carries chloride out of the intestinal contents without changing its concentration from that in the lumen while a fluid free of chloride moves from the blood into the intestinal lumen. If this theory is correct and deuterium oxide is a perfect indicator of active water movement, then R_o calculated from deuterium oxide absorption (R_{oD_2O}) should equal R_o calculated from chloride absorption (R_{oCl}) for an experiment in which deuterium oxide and chloride are simultaneously absorbed, chloride moving against a concentration gradient. Peters and Visscher (1939) found that R_{oD_2O} is greater than R_{oCl} and attributed this discrepancy to diffusion of deuterium oxide through pores other than those involved in active water movement and to the presence of chloride in the fluid passing into the intestinal lumen. In an attempt to evaluate the importance of diffusion in deuterium oxide absorption they carried out an experiment in which chloride, bromide, and deuterium oxide were absorbed, chloride only moving against a concentration gradient. The general fluid circuit theory (Peters, 1940) which includes diffusion and secretion of chloride and osmosis, suggests an analysis of this experiment which furnishes new evidence for the theory.

It is assumed that bromide and deuterium oxide are each absorbed by two first order processes proceeding side by side so that for either substance

$$dI/dt = C(dV/dt) + V(dC/dt) = -(a+d)C\,, \tag{1}$$

where I is the amount of the substance in the intestinal lumen, C its concentration, V volume, and t time. It is assumed that a is the constant for an active process and d is the constant for transfer by diffusion. Assuming further that

$$V = V_0 - Dt\,, \tag{2}$$

where D is the rate of volume decrease, we obtain by integration from equations (1)

$$CV/C_0V_0 = (V/V_0)^{(a+d)/D}, \tag{3}$$

where V is given by equation (2) and C_0 and V_0 are initial values for C and V.

From the original fluid circuit theory Peters and Visscher have derived the equation

$$CV/C_0V_0 = (V/V_0)^{R_o/D}, \tag{4}$$

where V is given by equation (2). Since equations (3) and (4) have the same form, R_o, calculated for bromide or deuterium oxide, has the significance indicated by the equation

$$R_o = a + d\,. \tag{5}$$

For bromide and deuterium oxide respectively we have

$$R_{oBr} = a_{Br} + d_{Br}\,, \tag{6}$$

$$R_{oD_2O} = a_{D_2O} + d_{D_2O}\,. \tag{7}$$

Using equations (4) and (2) Peters and Visscher (1939) found

$$R_{oBr} = 3.31 \text{ cc./min.}, \tag{8}$$

$$R_{oD_2O} = 4.13 \text{ cc./min.} \tag{9}$$

Since it is known that small amounts of chloride pass into the intestinal lumen under conditions closely approximating those of the experiment, R_{oCl} is calculated from the general fluid circuit theory. Using a simplified equation for the general theory (Peters, 1940, equation 11) we have

$$C(dV/dt) + V(dC/dt) = C_eR_i - CR_o\,, \tag{10}$$

where C_e is the effective chloride concentration of the fluid passing into the intestinal lumen at rate R_i. dV/dt, C_e, R_i, and R_o are here assumed to be constants.

If $dV/dt = -D$, then, from equation (10)

$$\frac{dC}{dt}=\frac{C_eR_i-CR_o+DC}{V}. \tag{11}$$

Substituting $dV/-D$ for dt and rearranging,

$$\frac{dC}{(R_o-D)C-C_eR_i}=\frac{dV}{DV}. \tag{12}$$

Since the solution placed in the intestine was isotonic and the experiment lasted only ten minutes, osmosis is assumed to be negligible and

$$D=R_o-R_i\,,\quad R_i=R_o-D\,. \tag{13}$$

Substituting R_o-D for R_i in equation (12) we obtain

$$\frac{dC}{C-C_e}+\frac{dV}{V}=\frac{R_odV}{DV}. \tag{14}$$

Integrating between the limits C_0 and C and V_0 and V,

$$\frac{(C-C_e)V}{(C_0-C_e)V_0}=\left(\frac{V}{V_0}\right)^{R_o/D}. \tag{15}$$

R_{oCl} can be calculated from this equation only if a value is assigned to C_e. The author (1941) has recently estimated upper limits for C_e from concentration-time curves for the accumulation of chloride in originally chloride free solutions placed in the lower ileum. An average upper limit of 0.018 per cent $NaCl$ and a maximum upper limit of 0.033 per cent were obtained in a series of eight experiments. Assuming that $C_e=0.018$ per cent $NaCl$ and applying equation (15) to the data of the chloride-bromide-deuterium oxide experiment we find that

$$R_{oCl}=2.15 \text{ cc./min.} \tag{16}$$

From equations (8), (9), and (16) we obtain the relations

$$R_{oD_2O}=1.92\,R_{oCl}\,, \tag{17}$$

$$R_{oBr}=1.54\,R_{oCl}\,. \tag{18}$$

Ingraham (1935) has shown that bromide and chloride are actively absorbed at the same rate, as would be expected from the fluid circuit theory. Since chloride is moving against a gradient in the present experiment, this may be expressed

$$a_{Br}=R_{oCl}\,. \tag{19}$$

From equation (6) we have

$$d_{Br} = R_{oBr} - a_{Br} . \qquad (20)$$

Substituting for R_{oBr} and a_{Br} from equations (18) and (19),

$$d_{Br} = .54\, R_{oCl} . \qquad (21)$$

In three experiments with rather porous collodion membranes at 37.5°, d_{D_2O}/d_{Br} ratios of 1.6, 1.7, and 1.9 were obtained. Assuming that the diffusion areas of the intestinal epithelium have the same permeability ratios as the average collodion membrane used, we have

$$d_{D_2O} = 1.7 d_{Br} \qquad (22)$$

and from equation (21)

$$d_{D_2O} = 1.7 \times .54 R_{oCl} = .92 R_{oCl} . \qquad (23)$$

From equation (7)

$$a_{D_2O} = R_{oD_2O} - d_{D_2O} . \qquad (24)$$

Substituting from equations (17) and (23),

$$a_{D_2O} = (1.92 - .92) R_{oCl} = 1.00\, R_{oCl} .$$

This is exactly what would be expected from the fluid circuit theory. If we assign to C_e the value for the maximum upper limit, 0.033 per cent $NaCl$, we obtain in the same way $a_{D_2O} = 1.04 R_{oCl}$ and if $C_e = 0$, we find $a_{D_2O} = 1.00 R_{oCl}$. If C_e is assumed to have the average value for the upper limit of 0.018 per cent and d_{D_2O}/d_{Br} is varied from 1.52 to 1.88, a_{D_2O} does not deviate from the theoretical value by more than ten per cent.

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THE GENERAL MEMBRANE EQUILIBRIUM EQUATION: ITS SIMPLE DERIVATION AND SOME OF ITS BIOLOGICAL IMPLICATIONS

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On the basis of thermodynamic considerations, expressions for the relation between the i-th and j-th ions and solvent separated into subsystems by a semi-permeable membrane are derived. From this basic equation expressions for the transfer of solvent attending solute changes are developed. The application of these expressions to biological systems involving solvent transfer, as in cellular growth, chloride shift in the red blood cell, imbibition of water into cells is discussed.

I. Introduction. In the usual thermodynamic derivation of the membrane equilibrium equation, it is tacitly assumed that no solvent is transferred across the membrane. (See for instance, Bolam, 1932.)[1] The fallacy of this assumption is apparent. In fact, the necessary transfer of water for maintaining osmotic equilibrium is explicitly stated in one of the classic applications of this theory to water and electrolyte balance between cells and plasma in blood (Van Slyke, 1923, and Henderson, 1928). Experimental determinations of the ratios, $[Cl^-]_c/[Cl^-]_s$, and $[HCO_3^-]_c/[HCO_3^-]_s$ have failed to satisfy the equality demanded by the simple equation (Van Slyke, 1923, and Henderson, 1928). In the present note there is first derived a basic relation between the i-th and j-th ions and the solvent, and then its implications of solvent transfer attending ion changes are studied (Donnan and Guggenheim, 1932).[2]

II. Derivation. We will begin by writing the chemical potential (partial molar free energy) of the i-th substance as a series of terms in which (at constant temperature) each variable term represents the energy above the standard energy possessed by i because of some type of work which has been performed upon it, e.g., osmotic, electrical, etc. For the system we are interested in:

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[1] This statement does not imply that the question of water transfer across membranes has been altogether neglected. See for example the important papers of Longsworth, 1933, 1934; Schreinemakers, 1933a, 1933b, and Liu, 1931 and 1932.

[2] The basic equation for the *sum* of positive and negative ions has already been given in this beautiful paper by Donnan and Guggenheim. However, their equation cannot be used to derive expressions for solvent transfer attending changes in particular electrolytes.

$$\mu_i = \mu_i^* + RT \log a_i + \pi \bar{V}_i + z_i F \psi . \qquad (1)$$

This symbolism requires some comment. μ_i^* is the standard chemical potential—the partial molar free energy when $a_i = 1$, $\pi = 0$, and $\psi = 0$. $\pi =$ the pressure acting throughout the phase; in particular this factor contains the osmotic term. In the usual derivation it is omitted, *implying the solvent cannot move from phase to phase.* z_i is the valence of the i-th ion. F is the Faraday constant, and ψ is the electrostatic potential of the phase. $\bar{V}_i$ is the partial molar volume of the i-th ion, $\bar{V}_i = (\partial V/\partial n_i)_{T,\pi,n_j}$, $j \neq i$ where V is the volume of the *system* and n_i is the number of moles of the i-th substance. Clearly $\bar{V}_i$ will depend on what substances are mixed with i in each particular concentration, and measurements of $\bar{V}_i$ must be made on a solution similar to the one being considered by the theory; its value is *not* merely molecular weight/density.[3] There are theoretical difficulties involved in obtaining $\bar{V}_i$ when i is an ion. This matter will be considered later (p. 155). a_i is the activity (referred to mole-fractions) of the i-th ion. Strictly speaking it is not possible, by thermodynamics alone, to obtain a_i for ionic substances, and the Lewis concept of mean ionic activities (Lewis and Randall, 1923) should be used. However, the Debye-Hückel theory does make possible the calculation; so that we will retain this form, bearing in mind the way in which a_i is to be obtained.

Using the form (1), Donnan and Guggenheim, 1932, have given the relation between solvent and i-th ion activities and, $\Delta \psi$ the membrane potential, or electrical potential difference between the two solutions;

$$\frac{1}{\bar{V}_1} RT \log \frac{a_1''}{a_1'} = \frac{RT}{\bar{V}_i} \log \frac{a_i''}{a_i'} + \frac{z_i F}{\bar{V}_i} \Delta \psi . \qquad (2)$$

Manipulating expressions for the j-th ion in a similar way and eliminating $\Delta \psi$ between the two equations of the type (2), we obtain:

$$\frac{1}{\bar{V}_1} \left(\frac{\bar{V}_i}{z_i} - \frac{\bar{V}_j}{z_j} \right) \log \frac{a_1''}{a_1'} + \frac{1}{z_j} \log \frac{a_j''}{a_j'} = \frac{1}{z_i} \log \frac{a_i''}{a_i'} . \qquad (3)$$

It is important to note that the first term of equation (3) represents a correction, as it were, on the simple membrane equilibrium equation;

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[3] It is unfortunate that this concept has been confused in otherwise good expositions. See, for instance, the calculation of Liu (1931) and of Adair (1937).

$$a''_j/a'_j = a''_i/a'_i\,. \tag{4}$$

III. Deductions. Ion Ratios: It is clear that equation (3) reduces to the simple form in the case that $\bar{V}_i/z_i = \bar{V}_j/z_j$ or if $a''_1 = a_1'$. In systems consisting of dilute solutions $a''_1 \cong a'_1$; however, systems wherein one phase contains non-permeant ions in fair amounts may present considerable deviations from this equality. Again, whenever a marked concentration of substances occurs, the ratio, a''_1/a'_1, will depart from unity and consequent deviations from the equilibrium ratios predicted by the simple equation would be expected. Cases in point are the well-known *Valonia* cells, Ascidian organisms, red blood cells, etc.

Numerical estimates of the term, $1/\alpha$ where

$$\frac{1}{\alpha} \equiv \frac{1}{\bar{V}_1}\left(\frac{\bar{V}_i}{z_i} - \frac{\bar{V}_j}{z_j}\right) \tag{5}$$

demand a knowledge of the partial molar volumes of *ions*. Partial molar volumes of individual ions exhibit the same thermodynamic indeterminacy as activities of individual ions. As in studying the latter, recourse to molecular theory may be helpful.[4] Partial molar volumes for electrolytes of biological importance, e.g., $NaCl$, KCl, etc. are of course readily available in the literature. We can proceed by postulating that for some electrolyte the $\bar{V}$ of the positive ion may bear some relation to the $\bar{V}$ of the negative ion. On the basis of the striking symmetry of KCl (e.g., equal migration velocity of the two ions in water, geometrical symmetry of KCl crystals, etc.) we assumed that in KCl,

$$\bar{V}_{K+} = \bar{V}_{Cl-} \tag{6}$$

and

$$\bar{V}_{K+} + \bar{V}_{Cl-} = \bar{V}_{KCl} = \text{known}\,. \tag{7}$$

One can then find the $\bar{V}$'s of other ions by the simple procedure of solving an equation of the type of (7). For instance,

$$\bar{V}_{\overset{+}{Na}} = \bar{V}_{NaCl} - \bar{V}_{Cl-} = \bar{V}_{NaCl} - \tfrac{1}{2}\bar{V}_{KCl}:$$

In this manner a table of "ionic partial molar volumes" can be built up. It may be remarked that cursory application of this procedure led to reasonable agreement between values for $\bar{V}_i$ calculated from the $\bar{V}$ of different compounds containing the i-th ion.

"Chloride shift": It is found experimentally that during the oxy-

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[4] We are indebted to Dr. W. F. Libby for valuable suggestions.

genation and reduction of hemoglobin in red blood cells, transfer of bicarbonate and chloride ions across the cell membrane occurs in opposite directions. This phenomenon is commonly known as the "chloride shift". Under these circumstances, water is simultaneously transferred. Despite this evidence of osmotic work, the simple equation $[Cl]_c/[Cl]_s = [BHCO_3]_c/[BHCO_3]_s$, as derived on the assumption that no osmotic work is done, has been traditionally used as an explanatory principle. Substitution in it shows quite obviously that either of the ion ratios varies *directly* with the other; i.e., Cl^- and HCO_3^- should transfer in the same direction, which is contrary to fact. However, if the general equation (3) is used, no such antinomy is reached, since the transfer of solvent can account for the passage of the two ions (Cl^- and HCO_3^-) in opposite directions.

Solvent Transfer: *A Suggested Mechanism*: The uptake and extrusion of water, e.g., water uptake in growth, etc., is common to all metabolizing cells. The mechanisms of this process may be various, but certainly equation (3) clearly indicates that changes in solute concentrations effect water transfers. (It should be noted that small changes in the activities of water involve relatively large *amounts* of water transferred, for the reason that water exists at a much greater concentration than any solute.) In this section we will derive simple expressions for the amounts of solvent transferred when the solute concentrations change in certain ways. All these expressions are for *small* variations in solute concentration. The method for obtaining the corresponding expressions for large variations is obvious. Let us suppose that f is the water concentration in a cell, and that it can be written as a function of two concentrations of solutes x and y. Thus:

$$f = f(x, y). \tag{8}$$

The increment in f attending small variations in x and y, is

$$\delta f = \left(\frac{\partial f}{\partial x}\right)_y \delta x + \left(\frac{\partial f}{\partial y}\right)_x \delta x . \tag{9}$$

The present treatment is made on the assumption that the cell is suspended in media which maintain constant concentration (infinite reservoirs). Double primes denote cell interior; single primes, the medium in which the cell exists. Furthermore, for the sake of formal simplicity, we will now assume ideal solutions, whence we may replace a_i by N_i.

A. Solvent Transfer with Ion Changes. (*i*) Solvent and Ion transfers: Rearranging equation (3) preparatory to differentiation and substituting from equation (5), we have

$$\log N_1'' - \log N_1' = (\alpha/z_i) \log (N_i''/N_i') - (\alpha/z_i) \log (N_j''/N_j') \; .$$

The increment in N_1'' is then given by

$$\delta (\log N_1'') = (\delta N_1''/\delta N_1'') = (\alpha/z_i)(\delta N_i''/N_i'') - (\alpha/z_j)(\delta N_j''/N''_j) . \tag{10}$$

Equation (10) is quite general, and gives the per cent changes in solvent mole fractions when the mole fractions of the *i*-th and *j*-th ions undergo variations, $\delta N_i''$ and $\delta N_j''$ respectively. These variations are not, however, completely independent. For electrical neutrality,

$$z_i \, \delta n_i + z_j \, \delta n_j = 0 \, , \tag{11}$$

where of course n_i and n_j represent the numbers of moles of the *i*-th and *j*-th substances. Now since the total number of moles, A, remains fairly constant we may divide equation 11 by A and obtain

$$z_i \, \delta N_i + z_j \, \delta N_j \cong 0 \, . \tag{12}$$

From equation (12) it follows that $\delta N_j = -\dfrac{z_i}{z_j} \delta N_i$.

Substituting into equation (10) we obtain

$$\frac{\delta N_1''}{N_1''} = \alpha \left(\frac{1}{z_i N_i''} + \frac{z_i}{z_j^2 N_j''} \right) \delta N_i'' . \tag{13}$$

Rearranging within the brackets of equation (13), and substituting within it the explicit value of α,

$$\frac{\delta N_1''}{N_1''} = \frac{\overline{V}_1}{z_j N_i'' N_j''} \left(\frac{z_j^2 N_j'' + z_i^2 N_i}{z_j \overline{V}_i - z_i \overline{V}_j} \right) \delta N_i'' \, . \tag{14}$$

If we change the *i*-th and the *j*-th mole fractions and the mole fractions of no other permeant ions or non-ionized substances, the per cent change in the mole fraction of solvent is given by the above equation (14). It might be well to pause here and consider how such a change may be brought about. Returning to equation (11) we see that z_i and z_j are of the same sign, n_i and n_j must be of opposite signs; in other words, the *exchange* of ions with the external medium can lead to solvent transfer. On the other hand, if z_i and z_j are of opposite signs, then n_i and n_j must be of the same sign, implying that the *transfer in toto* of an electrolyte also effects a solvent transfer. It might at first sight be thought that the apparently arbitrary changes we have just mentioned violate the mole fraction equation,

$$\sum_r N_r = 1 . \tag{15}$$

This is not the case, however, provided we realize that in equation (15) the summation must be made over *all* substances, and not only over the permeant ones. Into the expressions of the Donnan Equilibrium only the permeant substances enter. We might re-write equation (15) as follows:

$$\sum_{u} N_u(\text{impermeant}) + \sum_{\substack{d \neq i \\ d \neq j}} N_d(\text{permeant}) + N_i + N_j = 1. \tag{16}$$

In equation (16), N_i and N_j are changed according to our discussions; $\sum_d$ must remain constant by hypothesis, but $\sum_u$ can compensate the change in the i-th and the j-th substances and thus preserve the equality.

(ii) Changes in the Membrane Potential Attending Solvent and Ion Transfers: Since by rearranging equation (2) we have,

$$\Delta\psi = \frac{\bar{V}_i R T}{z_i F}\left(\frac{1}{\bar{V}_1}\log\frac{N_1''}{N_1'} - \frac{1}{\bar{V}_i}\log\frac{N_i''}{N_i'}\right)$$

it follows that

$$\delta(\Delta\psi) = \frac{V_i R T}{z_i F}\left(\frac{1}{\bar{V}_1}\,\delta\frac{N_1''}{N_1''} - \frac{1}{V_i}\,\delta\frac{N_i''}{N_i''}\right). \tag{17}$$

Substituting from equation (14) into equation (17),

$$\delta(\Delta\psi) = \frac{\bar{V}_i R T}{z_i N_i'' F}\left(\frac{1}{z_j N_j}\left\{\frac{z_j^2 N_j'' + z_i^2 N_i''}{z_j \bar{V}_i - z_i \bar{V}_j}\right\} - \frac{1}{\bar{V}_i}\right). \tag{18}$$

Equation (18) now gives the change in membrane potential when N_i and N_j vary subject to the conditions discussed above. It is clear that in general the changes occurring in our systems can be described by any two of the three functions: solvent transfer, ion transfer, membrane potential.

B. Solvent Transfer Attending Concentration Changes of Undissociated Substances. Donnan and Guggenheim, 1932, give the relation between the concentration of the u-th undissociated substance and the solvent as,

$$\frac{1}{\bar{V}_u}\log\frac{N_u''}{N_u'} = \frac{1}{\bar{V}_1}\log\frac{N_1''}{N_1'}. \tag{19}$$

Taking increments as before,

$$\frac{\delta N_1''}{N_1''} = \frac{\bar{V}_1}{\bar{V}_u}\,\frac{\delta N_u''}{N_u''}. \tag{20}$$

We can imagine that the mole fraction of the u-th substance may change either by uptake or by extrusion of the u-th substance, but perhaps biologically more important is the possible polymerization of the u-th substance into an impermeant material according to the reaction

$$m\,U_{(\text{permeant})} \rightarrow U_{n(\text{impermeant})}\,. \tag{21}$$

Implying of course, that

$$\delta N_u'' = m\,\delta N_{u_n}\,. \tag{22}$$

If m is very large, the effect of this mechanism of solvent transfer would be correspondingly marked. An interesting reaction which suggests itself is the so-called "dehydrolytic synthesis" of peptides, proteins, etc. In general if a peptide linked molecule contains m monoequivalent amino acids, $(m - 1)$ moles of water were produced by its polymeric synthesis. Thus, if $\delta N_{u_n}''$ is the increment in impermeant ion, the maximum increment in amino acid would be $m\,\delta N_{u_n}''$. (In the case where only one acid is involved), and the increment in water is $(m-1)\,\delta N_{u_n}'' = \delta N_i''$ (reaction). Now in equation (20),

$$\delta N_1'' = \delta N_1''_{(\text{reaction})} + \delta N_1''_{(\text{transfer})}\,.$$

So we may write:

$$\frac{\delta N_1''(\text{transfer})}{N_1''} = \frac{\bar{V}_1}{\bar{V}_u}\,\frac{\delta N_u''}{N_u''} - \frac{\delta N_1''}{N_1'}\,(\text{reaction}) \tag{23}$$

multiplying and dividing the last term in equation (23) by $\delta N_{u_n}''$, and remembering $N_1''(\text{reaction})/N_u'' = m-1/m$, we have

$$\frac{\delta N_1''(\text{transfer})}{N_1''} = \left(\frac{\bar{V}_1}{\bar{V}_u N_u''} - \frac{m-1}{m\,N_1''}\right)\delta N_u''\,. \tag{24}$$

In cases where the molecule is being polymerized from more than one acid, similar though more awkward expressions than equation (24) could be at once written down merely by breaking up the N_1'' into fractions.

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BOOK REVIEWS

HANS SCHAEFER. *Elektrophysiologie. I. Band. Allgemeine Elektrophysiologie.* Vienna: Franz Deuticke, 1940, XI + 522 pp. 94 figs.

BERNHARD KATZ. *Electric Excitation of Nerve.* London: Oxford University Press, 1939, IX + 151 pp. 31 figs.

An unsuspecting reader opening either of these excellent volumes at random would very likely think that he had before him a physics monograph rather than a physiology text. And, indeed, this is a very encouraging state of affairs, for each of these books abundantly proves that electrophysiology has finally and irrevocably adopted the method, if not the aim, of physics, both experimental and theoretical—so much so that electrophysiology is certainly one borderline field in which philosophic distinctions between biology and physics have been ignored.

The scope of Dr. Katz's book is considerably smaller than that of Prof. Schaefer, and, as a result, his exposition is somewhat more unified than the latter's. Beginning with some fundamental physiological observations (local summation, etc.), Dr. Katz proceeds to a formulation of the current two-factor excitation equations together with a discussion of their experimental support. The viewpoint is formal throughout, no particular assumption being made concerning the physical nature of the excitation parameters. In the second half of his book, Dr. Katz considers those aspects of nerve activity, such as electrotonus, conduction, local response, etc., which are manifestations of the kernleiter structure of the nerve. The viewpoint here can no longer be strictly formal, and Dr. Katz's attempt to incorporate the formal, linear excitation equations into a description of sub-liminal response leads to certain logical inconsistencies. Either one must follow Rushton and work out a completely physical theory which includes a unified discussion of both excitation and conduction, or one must ignore the kernleiter properties of the nerve and treat subliminal as well as superliminal responses on a purely formal phenomenological basis. The latter course leads to non-linear excitation equations, which, though complicated, seem to afford the possibility of including the phenomena of repetition and recovery into the mathematical description of nerve activity.

Prof. Schaefer's treatise (it contains no less than 6000 separate references, all neatly classified and indexed) takes its place as the obvious successor to Bernstein's Elektrobiologie and Biedermann's Elektrophysiologie. The work begins with a very complete survey of the passive-electric properties of living tissue and then goes on to an exposition, both mathematical and experimental, of the two-factor theory, and of local response. As in Dr. Katz's book, no consideration is given to the necessity for a non-linear modification of the theory to account for events occurring near excitation. Professor Schaefer identifies the parameter of excitation with the membrane potential difference, and this leads him tentatively to associate the process of accommodation with the spread of potential away from the site of excitation due to the geometry of the excitable structure. Such an assumption concerning accommodation is certainly conjectural; its mathematical consequences (which could be tested experimentally) have not been worked out yet.

A well-organized, clear discussion of the characteristics and possible origin of various biological potentials (demarcation potential, action potential, membrane potential) occupies almost a third of the text. It is a little disappointing that the theoretical discussions of conduction which have appeared at various times in the literature are barely mentioned; to this reviewer it seems that they are comparable in importance to the various excitation theories, since tentative conduction equations relating velocity, safety factor, and physical constants of nerve could serve as a framework for experimentation on conduction of the impulse in the same way that the two-factor theory has served for organizing data on excitation.

The volume ends with a consideration of synaptic transmission, and the effect of unphysiologic conditions on bioelectric phenomena. Professor Schaefer inclines very heavily toward an electrical interpretation of synaptic transmission, and he presents his evidence well. However, it should be pointed out that in a science as young as electrophysiology (one can argue that the modern science started with the advent of the cathode ray oscillograph) an author is apt, unconsciously to be sure, to allow his own experiments and interpretations to affect his judgment of the relative importance of the data of others; and, to some extent, Professor Schaefer seems to have fallen into this error whenever he contends that the excitation process "is" the recorded action potential.

But these are very minor criticisms for a work of this magnitude. This volume is, in the reviewer's opinion, the most important modern book on bioelectric phenomena to have appeared. It is sincerely hoped that some anonymous benefactor of English-speaking electrophysiologists will gain the everlasting gratitude of his colleagues by translating the book into English.

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